ROLE OF THE GONADS IN HYPERTENSION-PRONE RATS*

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In our genetically hypertension-prone strain of rats (1–3) we repeatedly observed that, while the ultimate blood pressure levels were similar in both sexes on a high salt diet, the males generally developed hypertension more rapidly than the females. A genetic study earlier had established that blood pressure control in these rats is multigenic (4); in that study there was no evidence that it was sex-linked but the previously noted influence of sex on blood pressure was confirmed.

The present study was based on those prior observations and was set up to answer the question: do the gonads play a role in the rate of development of hypertension? The results indicated that castration enhanced the rate at which hypertension developed in females. These findings might bear on the long-debated question of postmenopausal hypertension in human females.

Materials and Methods

Only rats from our hypertension-prone (S) strain were used in these experiments. Details on their origin, care, feeding, and measurement of blood pressure may be obtained from earlier publications (1, 2, 4–6) and, therefore, only items pertinent to this study will be included here. These rats rapidly develop a fulminating hypertension when placed on a "high" (8%) NaCl chow at weaning and most will be dead or dying after 6–12 wk on such a regimen. This rapid progression sometimes blurs the difference in response of the two sexes. If the high salt diet is postponed until some weeks after weaning, the disease in no less fatal but it develops more slowly (6) and, under these circumstances, the sex difference is more evident. In the present experiment, all rats were maintained on our special "low" (0.3%) NaCl diet until the experiments started; this chow contains sufficient sodium for normal growth and development.

40 male and 40 female rats, all 6 wk of age, (i.e., 3 wk postweaning) were divided among eight groups of 10 each in a 2 × 2 × 2 factorial design to test for the effects of diet (8% vs. 0.3% NaCl chow), sex, and castration: there were, therefore, four groups of each sex, intact or castrated, on high or low salt diets. Littermates were assigned randomly to different groups; all groups had similar initial average blood pressures; initial weights did not differ significantly ($P > 0.05$) among the four groups of males and of females, respectively. Gonadectomy was performed under ether anesthesia on the first day of the experiment. Systolic blood pressures and weights were measured biweekly among those on 8% NaCl and, after the 4th wk, at monthly intervals in the groups on 0.3% NaCl when it had become evident that gonadectomy alone did not result in fulminating hypertension. Blood pressures were followed for at least 36 wk unless an animal died or was sacrificed earlier because of its moribund state. Final systolic blood pressures used in the statistical comparison of means were cumulative, i.e., the pressure at the end either of the experimental period or the last pressure while an animal was in good health was carried forward

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whether the rat died after a few weeks or near the end of the experiment. "Good health" was defined as maintenance of weight with a loss of no more than 10 g from any earlier maximum weight (4, 6). Data were analyzed by analysis of variance using a special computer program.[1] Difference in means with P values < 0.05 were considered significant and all P values < 0.01 were assigned that nominal value.

Results

Survivorship (Table I). Among the four groups on high NaCl, deaths commenced after the 4th wk; by the 18th wk, of the original 40 rats, only four, all intact females, remained alive with the last two dying shortly after the 24th wk. Castration had no clear-cut effect on survival of males but was associated with significantly shortened life-expectancy in the females: at 12 wk, when there were no survivors in the castrated group, eight of the original 10 intact females were still in good health. This different response was probably related to the higher blood pressure of the castrated females (see below).

The four groups on low NaCl had significantly longer survival than those just described on high NaCl: at 20 wk, for instance, when only 4 of the original 40 rats on high NaCl were still alive, 38 of the 40 on low NaCl remained in good health. These intact females on low NaCl, like those on high NaCl, again demonstrated the best survivorship with but one death when observations were terminated after 36 wk. The other three groups on low NaCl had distinctly greater mortalities than the intact females particularly after the 24th wk and by the 36th wk, 20 of the original 30 in these three groups were dead.

Growth Curves

FEMALES (Fig. 1). The two female castrate groups grew more rapidly and attained significantly greater weights as compared with the two intact groups. This was manifest by the second week ($P < 0.05$) and the difference increased thereafter ($P < 0.01$). Both of these castrate groups grew at similar ($P > 0.05$) rates through the 8th wk: comparisons were not made thereafter since there were only two survivors in the high salt group at 10 wk and none by the 12th wk. Growth curves were also similar ($P > 0.05$) for the two intact groups through the 20th wk, after which no comparisons were made since there were only two survivors in the high salt group at 24 wk and none by 28 wk.

MALES (Fig. 2). The growth pattern of the males was dissimilar from that of the females: among the rats on either high or low NaCl, the castrate animals grew less rapidly than the comparable intact rats. This difference was significant ($P < 0.01$) by the end of the 2nd wk and continued thereafter as long as comparisons could be made which, in the two groups on high NaCl, was through the 12th wk, after which there were no survivors in the castrate group. The two groups on low NaCl, by contrast, had sufficient survivors at 36 wk to make a significant comparison. Again in contrast to the females, males on high NaCl weighed less than those on low NaCl: this was significant ($P < 0.01$) by the 10th wk for the castrate groups, by the 8th wk ($P < 0.01$) for the intact groups.

Effect of Gonadectomy on Blood Pressures

HIGH NACL (Fig. 3). All 40 of the rats in the four groups on high salt became

[1] We thank Keith Thompson for the statistical analyses.

TABLE I

Effect of Sex, NaCl, and Castration on Survivorship

Sex	Diet	Castration	Week ..	No. of survivors																	
				0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
M	High NaCl	+		10	10	10	9	7	4	4	0											
M	High NaCl	–		10	10	10	8	6	4	4	4	2	0									
F	High NaCl	+		10	10	10	8	7	2	0												
F	High NaCl	–		10	10	10	10	9	8	8	5	4	4	4	3	2	0					
M	Low NaCl	+		10		10		10		10		9		9		9		8		7		5
M	Low NaCl	–		10		10		10		10		9		9		8		5		5		3
F	Low NaCl	+		10		10		10		10		10		10		8		7		6		2
F	Low NaCl	–		10		10		10		10		10		10		10		10		10		9

All rats were from the hypertension-prone (S) strain. Both sexes were maintained on low (0.3%) NaCl chow until they were castrated at 6 wk of age which is considered week zero. Immediately after castration, for half of the rats the diet was changed to high (8%) NaCl chow while the other half remained on low NaCl chow. Both diets continued without change until the experiment was terminated after 36 wk. There were 10 animals in each group initially.

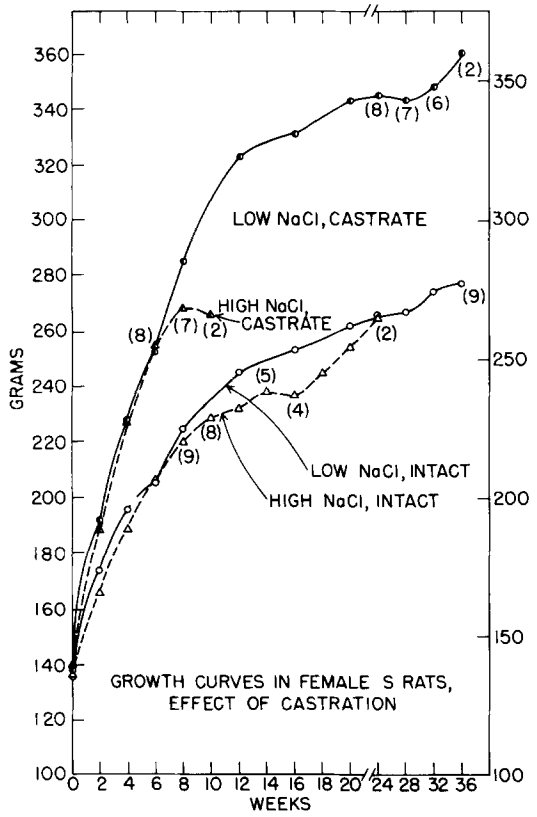

FIG. 1. The two castrate groups of females weighed more than the two intact groups by the second week ($P < 0.05$) and the difference increased thereafter ($P < 0.01$). The two castrate groups grew at similar rates ($P > 0.05$) through the 8th wk beyond which comparisons were not made. The two intact groups were similar through the 20th wk. Initially each group had 10 members. Numbers in parentheses indicate survivors.

hypertensive. In conformity with our previous experience (4), the 10 intact males rapidly developed fulminating hypertension as shown by an average systolic blood pressure of 194.9 ± 4.20 mmHg (mean ± SEM) by the end of the 10th wk. Gonadectomy appeared to be without influence in males since the rate at which hypertension developed and the level attained did not differ significantly from the intact males just described (194.9 ± 7.21 mmHg at the 10th wk).

Among the two groups of females, the results were at variance with the males in that gonadectomy clearly modified the course of development of hypertension. The intact females behaved as we usually have noted in earlier observations: blood pressure rose more slowly than in males but, ultimately, reached the same levels. At 10 wk, mean systolic pressure was only 162.8 ± 8.70 mmHg; by the 16th wk blood pressure had increased to 184.4 ± 11.2 mmHg, and by the 20th wk to 200.9 ± 7.66 mmHg. The castrated females behaved differently: the course of their hypertension replicated with remarkable similarity that in the two groups of S males described above: after 10 wk the average systolic pressure was 198.0 ± 7.33 mmHg. Blood pressures for the two groups of males and the castrated

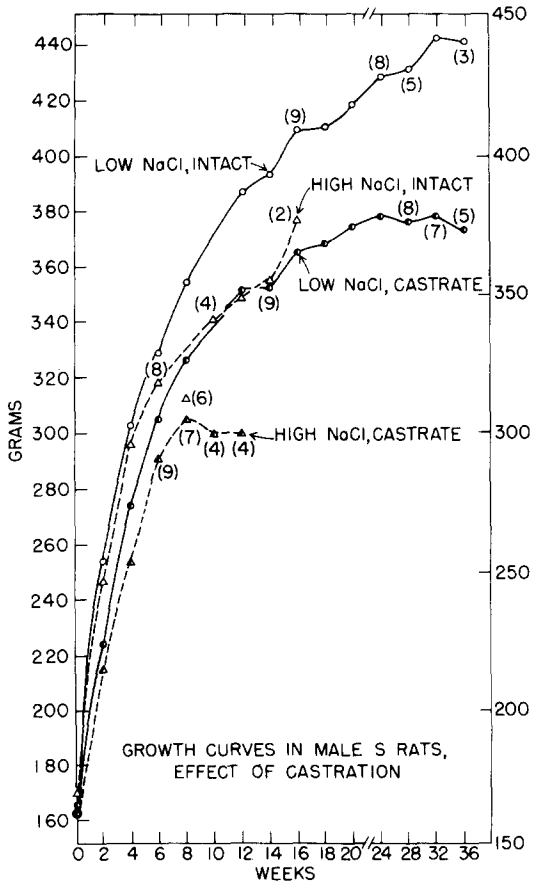

FIG. 2. The two castrate groups of males weighed less than their comparable intact groups by the end of the 2nd wk ($P < 0.01$). In contrast to the females, males on high NaCl weighed less than those on low NaCl: by the 8th wk ($P < 0.01$) for the intact groups and by the 10th wk ($P < 0.01$) for the castrate groups. Initially each group had 10 members. Numbers in parentheses indicate survivors.

females are not shown after 10 wk in Fig. 3 since there were no survivors at 12 wk in the castrated females. There was no significant difference ($P > 0.05$) in the blood pressures among these last three groups.

Low NaCl (Fig. 4). Among these four groups of rats blood pressure data were analyzed through the 36th wk of the experiment. The general patterns of response resembled those of similar rats on high NaCl except that average pressures were lower and survival longer. Most of the S males slowly developed mild hypertension despite the low salt diet, a phenomenon that we have noted before in these rats (4, 6–8). Gonadectomy did not appear to influence either blood pressure or survival in males. After 36 wk of observation, the intact males averaged 159.7 ± 8.42 mmHg whereas in the castrated males the figures were 167.9 ± 9.92 mmHg ($P > 0.05$).

Intact females generally remained normotensive at the end of the 36th wk and averaged 128.8 ± 2.89 mmHg; whether pressures in this group would ultimately

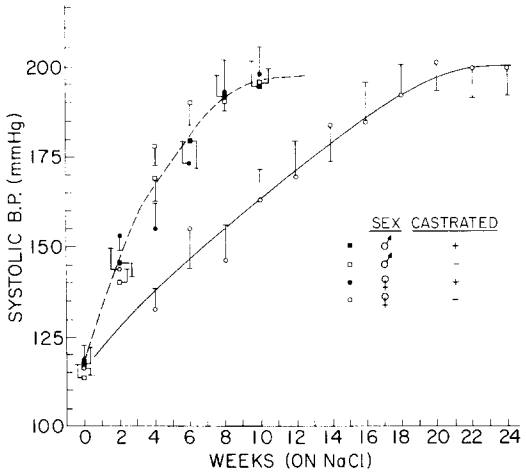

FIG. 3. Effect of castration on blood pressure of S rats all on high NaCl diet. There was no significant difference ($P > 0.05$) among the intact males (□), castrated males (■) and castrated females (●). After the 4th wk the intact females remained lower than the other three groups until after the 14th wk.

have reached the same level as males, as was the case with intact females on high salt, cannot be deduced from these data. Gonadectomy of these low salt females resulted in the same degree of mild hypertension at the end of the study observed in the two groups of low salt males: 161.8 ± 5.00 mmHg ($P > 0.05$).

In summary, castration was without effect on the blood pressure of males. In females, however, castration changed the blood pressure response so that it was indistinguishable from that of males; in females on high salt, the normally slower development of hypertension as compared with males was speeded up and in those on low salt, a normotensive pattern was replaced by one of mild hypertension similar to that in males.

Discussion

In this animal model, gonadectomy caused the normally more slowly developing hypertension of salt-fed female rats to accelerate so that it was indistinguishable from that observed in males. Gonadectomy was without influence on the blood pressure of males.

Although there are innumerable papers dealing with blood pressure and female sex hormones, the effect of gonadectomy has been less commonly studied. In observations that seem relevant to ours, Ringer, Sturkie, and Weiss (9) reported that both intact and castrated male chickens had similar but significantly higher blood pressures than intact females after 8–12 wk of age; castration of females caused their pressure to rise to that of the males. Aoki (10) found that gonadectomy was without effect on either the later pressure of prehypertensive rats from the strain with spontaneous hypertension or on established hypertension in members of this same strain.

Reports of the effect of the administration of estrogens and progestogens on blood pressure are legion and review of the results suggests that under some

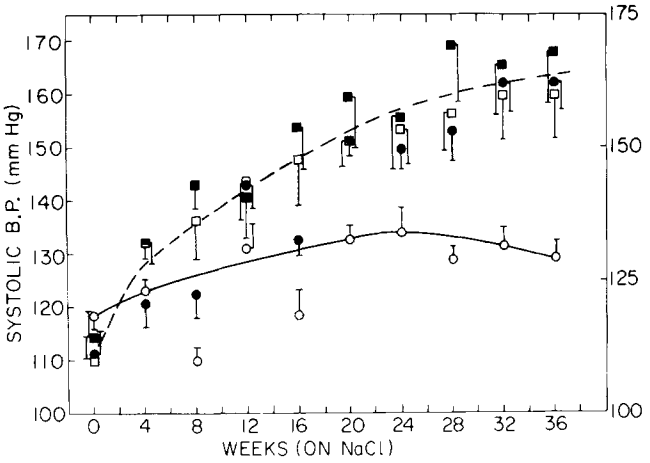

FIG. 4. Effect of castration on blood pressure of S rats all on low NaCl diet. After the 8th wk, there was no significant difference ($P > 0.05$) among the intact males (□), castrated males (■) and castrated females (●). The intact females (○) were lower than the other three groups from the 14th wk (not shown) on.

circumstances these hormones have hypotensive effects while under others they have definite hypertensive actions. This is indicated by the following examples which could be amplified without clarification of the role of female sex hormones in experimental hypertension. Thorn and Harrop (11) first reported that all the sex hormones they tested had a sodium-retaining effect of which estradiol and progesterone were the most active in this respect. Grollman, Harrison, and Williams (12) subsequently found that administration of estradiol, progesterone, and diethylstilbestrol to normal adult rats of both sexes caused elevation of pressures to hypertensive levels in some of the animals. Page and Ogden (13) found no effect on the pressure of normo- or hypertensive rats from the administration of estrogen or progesterone. Sturkie and Ringer (14), working with the hypertensive chickens referred to earlier, found that diethylstilbestrol depressed the blood pressure of intact males and capons but not of females. Armstrong (15) found that in five of six rats with renal hypertension, progesterone administration had a hypotensive effect. Similar effects were noted in two dogs with renal hypertension as well as in three human females with "primary arterial hypertension". Horrobin (16), by contrast, reported that long-term progesterone treatment in rabbits resulted in elevated pressures in all. Aoki (17), using the spontaneously hypertensive rat, reported that diethylstilbestrol, estradiol, and progesterone failed to elevate the pressure of either males or females but progesterone and estradiol may have had a hypotensive effect. Leathem and Drill (18) administered diethylstilbestrol to nine normotensive rats and observed a gradual rise in pressure in eight. In relatively short-term experiments Winter et al. (19) failed to observe a change in blood pressure in either rabbits or rats from the administration of progesterone. In our "S" strain of rats with genetic susceptibility to hypertension, when combined with an elevated NaCl intake administration of one combination of contraceptive steroids was hypertensinogenic whereas it was not in the absence of the NaCl (8).

Such factors as dosage, duration of exposure, synthetic vs. natural compounds, single hormone vs. combinations of both, animal species, and individual susceptibility probably all play a role in determining the blood pressure response to these steroids.

The observations of Helmer and Griffith in 1952 first demonstrated that administration of estrogens to rats caused an increase in plasma renin substrate (20). Since then considerable evidence has accumulated suggesting a relationship between one or more components of the renal pressor system and the sex hormones (21). Menard and Catt (22) summarized the general effects of estrogen treatment on the renin-angiotensin system as follows: plasma renin substrate is increased, plasma renin activity is often elevated, blood angiotensin is increased, and plasma renin concentration is usually decreased. Nasjletti et al. (21) reported that castration decreased renin substrate in estrus but not in diestrus female rats and had no effect in males; castration was also without effect on plasma renin concentration. Bing and Jørgensen also found that castration was without effect on renin substrate in rats of both sexes (23). But if it is by the administration of female sex hormones that changes in the renin-angiotensin system have been effected—sometimes with the development of hypertension—and if by castration no changes in components of this renal pressor system occur, it is difficult to ascribe the elevation in pressure observed in our castrated female rats to primary effects on the renin-angiotensin system.

We are led to speculate on the possible role of growth hormone in the pathogenesis of this enhanced rate of blood pressure development. More than forty years ago, Evans and Simpson (24) described the effect of gonadectomy on the weight and growth (length in cm) of rats: in the male, castration resulted in lower weights and lesser growth than in intact controls whereas in females the opposite was true: the castrates were heavier and longer than their controls. We did not measure length in our rats but observed the effects on weight described by Evans and Simpson. It therefore seems highly probable that similar changes in length occurred. Such effects could be interpreted to indicate that castration in the female causes a net increase in growth hormone output by the pituitary or, possibly, an increased sensitivity to its growth-promoting effects. In the male, castration would, according to this interpretation, result in the opposite effect on growth hormone. There are a few data which, if they do not confirm, at least are in line with such an interpretation. Birge et al. (25) reported that castration of the male rat caused a significant drop in radioimmunoassayable growth hormone in the pituitary; in the female, castration resulted in an increase that did not attain statistical significance. Catt and Moffat (26) observed that estrogens reduced the rate of growth hormone synthesis by the anterior pituitary, from which we might infer that castration of the female would enhance such synthesis. And MacLeod, Abad, and Eidson (27) reported that male rats had a greater rate of in vitro synthesis of growth hormone than did females; estrogen had no effect in males but caused a 25% decrease in growth hormone biosynthesis per milligram of pituitary gland in females although because the pituitary gland enlarged, the total amount per gland was the same. Perhaps most important of all, Sinha et al., using a sensitive radioimmunoassay for mouse growth hormone, reported that ovariectomy in female mice increased pituitary and serum concentrations of growth hormone to male levels (28).

If castration does enhance growth hormone output in the female, would this enhance the development of hypertension? Selye originally observed that administration of somatotrophic (i.e., growth) hormone to rats resulted in hypertension (29). Therefore, it is conceivable that growth hormone is involved in the increment in hypertension seen in these castrate females. If this is true, perhaps we should also have a slight decrement in the rate at which hypertension developed in castrate males, which we did not.

A second possibility is that along with their increased growth, the females ate more food and hence, necessarily consumed more NaCl. We think this explanation is unlikely because the effect of castration on blood pressure was also seen in the females on low NaCl food in which if salt intake was also increased, it was so slight as to be inconsequential in promoting hypertension.

The rise in pressure observed in these female rats with cessation of ovarian function might bear on the long-debated and controversial question of "menopausal" hypertension. Textbooks concerned with hypertension either do not mention this syndrome or do so to dismiss it. From review of the world literature, based for the most part on uncontrolled observations, it is clear that many older clinicians considered that there was such an entity (30). Numerous other studies (e.g., 31–33) have failed to support the concept. Recently, von Eiff et al. (34) discussed postmenopausal hypertension and proposed the hypothesis that ovarian hormones may have a "protective mechanism" for the blood pressure of females.

Our experiments lead us to propose the following: the menopause commonly manifests itself during the fifth and sixth decades of life, a time coinciding with the most frequent diagnosis of hypertension. Separation of the two phenomena is difficult since both are usually gradual in onset. But among those women with genetic susceptibility to hypertension, i.e., those who would in all probability have developed it during the next decade, an increase in growth hormone associated with declining ovarian function in the menopause could provide the stimulus for the appearance of hypertension some years earlier than might otherwise have been the case. We are aware of no studies on growth hormone during the human menopause that might support, or refute, this proposal. Our experiments suggest that this early development of hypertension would be more evident among those on a high rather than on a low salt intake.

Summary

In a genetically hypertension-prone (S) strain of rats it was observed previously that males generally developed hypertension more rapidly on a high salt diet than did females although final pressures ultimately were similar in both sexes. A genetic study had shown that there was no sex-linkage involved in setting blood pressure levels, so it was thought that the gonads might be involved. In the present work, castration of males had no effect on blood pressure but in the females it caused a rise in pressure that could not be distinguished from that in males, both on a high and low salt diet.

Castration resulted in greater growth in females than in controls, whereas it had the opposite effect in males. It was speculated that these changes were due to influences on pituitary growth hormone with castration increasing the net

output of growth hormone (or enhancing receptor sensitivity to it) in the female and the opposite in the male. From the work of others, there are some data compatible with such an interpretation. Experimentally, growth hormone will induce hypertension in rats. Therefore, it is conceivable that growth hormone is involved in the increment in hypertension observed in these castrate females.

Because the effect on blood pressure was observed in castrate females on both high and low NaCl diets, it was considered unlikely that the blood pressure effect was simply due to increased NaCl intake in the food associated with greater growth.

It was suggested that this rise in blood pressure with cessation of ovarian function might bear on the unsettled question of "menopausal" hypertension in women: in the genetically susceptible individual an increase in growth hormone associated with declining ovarian function in the menopause could provide the stimulus for the appearance of hypertension some years earlier than would otherwise have been the case.

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